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<b>(21) International Application Number:</b> PCT/US95/03330 <b>(22) International Filing Date:</b> 14 March 1995 (14.03.95)  <b>(30) Priority Data:</b> 08/213,542                      15 March 1994 (15.03.94)                      US  <b>(71) Applicant:</b> CHILDREN'S HOSPITAL OF LOS ANGELES [US/US]; 4650 Sunset Boulevard, Los Angeles, CA 90054-0700 (US).  <b>(72) Inventor:</b> KAUFMAN, Francine; 1401 North Bundy Drive, Los Angeles, CA 90049 (US).  <b>(74) Agent:</b> SCHIFFMILLER, Martin, W.; Kirschstein, Ottinger, Israel & Schiffmiller, P.C., 551 Fifth Avenue, New York, NY 10176-0024 (US).		<b>(81) Designated States:</b> AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA, UZ, VN, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG), ARIPO patent (KE, MW, SD, SZ, UG).  <b>Published</b> <i>With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
<b>(54) Title:</b> USE OF COMPLEX CARBOHYDRATE TO DIMINISH HYPOGLYCEMIA IN PATIENTS WITH DIABETES MELLITUS  <b>(57) Abstract</b>  Blood glucose levels in patients with Diabetes Mellitus is stabilized at 60 mg/dl for at least 6 hours by ingesting a complex carbohydrate, preferably uncooked cornstarch, in the dose of about 0.1 to 1.0 gram per kilogram of body weight.		

**USE OF COMPLEX CARBOHYDRATE TO DIMINISH  
HYPOGLYCEMIA IN PATIENTS WITH DIABETES MELLITUS**

**BACKGROUND OF THE INVENTION**

**1. *Field of the Invention***

5 This invention relates to therapeutic treatments of diabetes mellitus. More particularly, this invention relates to the use of uncooked cornstarch in the treatment of hypoglycemia caused by Type I and Type II diabetes mellitus.

**2. *Description of Related Art***

10 Symptoms of hypoglycemia fall into two main categories. Rapid epinephrine release causes sweating, tremor, tachycardia, anxiety, and hunger. Central nervous system symptoms include dizziness, headache, clouding of vision, blunted mental acuity, confusion, abnormal behavior, convulsions, and loss of consciousness. When  
15 hypoglycemia is recurrent or severe, nervous system symptoms predominate, and the epinephrine phase may not be recognizable. With more rapid drops or wide swings in plasma glucose (as in insulin reactions), adrenergic symptoms are prominent (*Harrison's Principles of Internal Medicine*, 11th Ed., McGraw-Hill Book Company, New York,  
20 1987, p. 1800).

Numerous strategies have been developed to achieve the goal of maintaining blood glucose at a relatively constant level, such as open looped continuous subcutaneous insulin pumps and multiple daily injections of insulin. These intensive insulin regimens are coupled with  
25 home glucose monitoring, and many patients measure their blood

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glucose levels by finger prick up to 6 to 8 times per day to assure that close to normal blood sugar levels are maintained. This regimen is prescribed because studies have shown that by avoiding excessive high blood sugar levels, the long-term outcome of patients with diabetes can be improved. However, this regimen, which decreases episodes of high blood sugar, also causes patients to experience more low blood sugar reactions (hypoglycemia). Results of the Diabetes Complication and Control Trial indicate that intensive insulin treatment, while it markedly delays and lessens long term retinal, nephrologic and neuropathic disease, leads to a three to nine-fold increase in hypoglycemic events, most of which occur at night (L.Y. Dawson, *Clinical Diabetes*, 11:88-96, 1993). Sometimes these episodes of hypoglycemia are severe and can lead to loss of consciousness and convulsions. Severe hypoglycemic events seem to occur more often at night while the patient is asleep rather than during the day. When awake, diabetic patients can feel hypoglycemic reactions beginning, and can treat themselves with sugar in order to bring their blood sugar levels back into the normal range. When asleep, patients do not have this awareness, therefore the risk of hypoglycemic is much higher during this time.

The need exists to develop strategies to diminish hypoglycemia while continuing to intensively manage diabetes. Cornstarch has been used effectively to combat the hypoglycemia associated with glycogen storage disease type 1, a disease having an inherited absence or deficiency of glucose-6-phosphatase activity in the liver, kidney, and intestines, leading to accumulation of glycogen in those organs and hypoglycemia during fasting. Protection against low blood sugar was provided for up to 6 to 8 hours after ingestion of uncooked cornstarch

(J. I. Wolfsdorf, *et al.*, *Am. J. Clin. Nutr.*, 52:1051-7, 1990). However, the dosage of cornstarch used for this treatment was 1.75 grams per kilogram of body weight. This dosage is much higher than could be tolerated by a patient with diabetes mellitus.

- 5 Another study has also been conducted in patients with diabetes, giving cornstarch during inpatient hospitalization, with a reduction in the nadir of the blood glucose level. Children were fasted and then given the entire carbohydrate content of the standard bedtime snack (30 grams of carbohydrate) as uncooked cornstarch (M.T. Ververs, *et al.*,  
10 *Eur. J. Clin. Nutr.*, 47:268-73, 1983). However, this study did little to prevent hypoglycemia and did not evaluate varying dosages to determine maximal efficacy.

Thus, the need exists for a better method of treating hypoglycemia in diabetics whether it results from too large a dose of insulin in patients  
15 with Type II diabetes who use insulin, or whether it occurs in patients with Type I diabetes, such as in pediatric patients during sleep.

## SUMMARY OF THE INVENTION

Blood glucose levels in patients with Diabetes Mellitus is regulated and stabilized by ingesting a complex carbohydrate, preferably uncooked  
20 cornstarch, in the dose of about 0.1 to 1.0 gram per kilogram of body weight.

A pharmaceutical composition being a preparation of a unit dose of uncooked cornstarch is also provided.

## A DETAILED DESCRIPTION OF THE INVENTION

This study will attempt to determine if uncooked cornstarch, given in a dose of 1.0 gram per kilo added to milk (equivalent to 25-50% of the evening snack carbohydrate calories) can diminish the incidence and severity of hypoglycemia in hospitalized patients receiving subcutaneous insulin and in outpatients while on their usual insulin regimens.

This invention provides a method of utilizing complex carbohydrates, and in particular, uncooked cornstarch, to stabilize glucose levels in patients by titrating the dosage so as to avoid both hyper- and hypoglycemia, for in diabetics hyperglycemia can be caused by ingestion of too much carbohydrate. In particular, this invention provides a method for administering to a diabetic patient a measured dose of complex carbohydrate, preferably in the form of uncooked cornstarch, to stabilize blood sugar levels above that generally identified with the onset of clinical symptoms of hypoglycemia. The definition of the onset of clinical symptoms of hypoglycemia as used herein is a blood glucose level less than or equal to 3.0 mmol/liter or 60 mg/deciliter of whole blood.

In the practice of this invention, uncooked cornstarch is the preferred source of complex carbohydrate since its carbohydrate content is relatively uniform, its rate of metabolism is both known and uniform, and can be readily formulated into easy to administer tablets, syrups (sweetened with synthetic sweeteners), coatings, etc.

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Diabetic patients cannot tolerate the high dosage of uncooked cornstarch used in the treatment of glycogen storage disease without developing hyperglycemia. The preferred dose of complex carbohydrate administered to a diabetic patient to forestall development of the clinical symptoms of hypoglycemia is, therefore, much lower, about 0.1 to 1.0 gram per kilogram, more preferably about 0.25 to 0.5 grams per kilogram of body weight.

In addition, in children under the age of two years, it is also preferred that the dosage of complex carbohydrate be administered together with the enzyme pancrease in an amount useful to promote digestion of complex carbohydrate. The pancrease is given adjunctively, usually in a dosage of about 1/4 teaspoon of pancrease per dose of complex carbohydrate.

All patients taking insulin to facilitate post-prandial absorption of glucose can be treated recurrently during the day with premeasured doses of complex carbohydrate that is slowly metabolized to the monosaccharide glucose over a period of six to eight hours instead of being treated with simple carbohydrates, such as orange juice or other sugar sources that tend to cause a rapid peak in blood glucose level that quickly subsides. During waking hours the patient's use of, and hence requirement for, glucose is varied and depends upon the level and type of activity. The exact amount and frequency of the actual dose, therefore, will vary by patient and from day to day for each patient. A blood glucose test, usually administered as a finger prick to obtain a blood sample, can be used to monitor daily glucose levels as well as the patient's own subjective experience of symptoms associated with the onset of hypoglycemia. Therefore, in the practice

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of this invention sufficient complex carbohydrate is administered, preferably in the form of uncooked cornstarch, to maintain the blood glucose level somewhat above this level.

5 To prevent hypoglycemia during overnight sleep periods, the complex carbohydrate is administered to the patient at bedtime, and the above described dose of uncooked cornstarch is sufficient so the patient passes the nocturnal sleep time without need for glucose intervention and awakens after about six to eight hours of sleep with a glucose level of 60 mg/dl or greater. Many diabetics routinely consume a standard  
10 bedtime snack containing about 30 grams of carbohydrate, such as bread, or cereal and milk. In the practice of this invention, about 1/4 to 1/2 of the bedtime carbohydrate snack is replaced by uncooked cornstarch to stabilize blood sugar levels through the night (for six to eight hours) and to wear off in time for the patient to awaken with a  
15 normal blood sugar level.

For convenience in measuring the dosage actually consumed, it is preferred that the complex carbohydrate be prepared in unit dosage forms of 5 grams each. The unit dosage can be formulated as tablets, lozenges, capsules, and the like, using techniques well known in the  
20 art. To assure proper metabolism of the complex carbohydrate, it is also preferred that the it be consumed together with at least two other food exchanges selected from the group consisting of fat, protein and other carbohydrates. For instance, cornstarch is routinely used as a binder in formulation of tablets (see *Remington's Pharmaceutical*  
25 *Sciences*, 18th Edition, Mack Publishing Company, 1990, pp. 1633-1675). It is preferred that ingredients in addition to uncooked

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5 cornstarch used in the formulation be inert to metabolism, such as  
cellulosic binders and the like, or, if not inert, that the nutritional  
contribution of such formulation ingredients to the carbohydrate  
content of the unit dosage be taken into account in formulating the unit  
dosage. In an alternative embodiment, the unit dosage formulations  
of complex carbohydrate used in the practice of the method of this  
invention are in the form of sustained release tablets, pills, lozenges,  
and the like. Sustained release formulations can be prepared in the 5  
gram unit dose form using techniques well known in the art  
10 (*Remington's Pharmaceutical Sciences, supra*, pp 1676-1686. In yet  
another embodiment of this invention, the uncooked cornstarch is  
incorporated into a snack bar containing a total of about 30 grams of  
carbohydrate (comparable to prior art bedtime snacks for diabetics),  
but having about 1/2 to 1/4 of the carbohydrate in the snack be  
15 uncooked cornstarch in the form of a filling or coating, for example, one  
sweetened with a non-sugar sweetener.

The following examples illustrate the manner in which the invention can  
be practiced. It is understood, however, that the examples are for the  
purpose of illustration and the invention is not to be regarded as limited  
20 to any of the specific materials or conditions therein.

### EXAMPLE 1

Forty patients with Type I Diabetes Mellitus who were receiving  
subcutaneous insulin hospitalized at Children's Hospital of Los  
Angeles or were seen in the Endocrine Outpatient Clinic and were  
25 receiving their usual insulin regimens were asked to participate in a  
study to determine whether administration of uncooked cornstarch



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as part of the evening snack would diminish the incidence and severity of hypoglycemia. On day one, ten patients, 2 to 25 years of age were treated as inpatients and patients received 1.0 gram/kg of body weight of uncooked cornstarch (Arrow Cornstarch) in milk as part of the bedtime snack. Hourly bedside blood glucose determinations were done from midnight until 6 a.m. by fingerstick requiring a single drop of blood. In addition, observable symptoms of hypoglycemia, such as thrashing about or convulsions were recorded. If significant hyperglycemia was experienced, the dosage of uncooked cornstarch for day two was reduced to 0.5 g/kg. If on the other hand, significant hypoglycemia was experienced, on day two the dose was increased to 1.5 grams/kg. In addition, an oral report of the patient's observable nighttime symptoms was made either by the patient or its parent to an attending physician at least three times per week to monitor the patient's progress on the study. Data was compared to inpatient records for the last two years and matched by age, sex and duration of diabetes.

Patients treated as inpatients of Children's Hospital Los Angeles has a significant reduction in middle of the night hypoglycemia while receiving the cornstarch-containing snack compared to the regular snack. There was no significant elevation of the blood glucose level after ingestion of the cornstarch-containing snack as would be seen with simple carbohydrates.

Thirty patients, 2 to 25 years of age, were tested as outpatients. Blood sugar tests were conducted prior to bed, at 2 to 3 a.m., and in the morning when awakened. The three blood sugar level readings were recorded for a two week period during which the patient received the

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standard bedtime snack containing 30 grams of carbohydrate containing no cornstarch. During the following two week period, the same regimen was followed except that 25 to 50% of the carbohydrate portion of the evening snack administered at bedtime was uncooked cornstarch. Once again blood sugar levels were measured and recorded just prior to bed, at 2 to 3 a.m., and in the morning when awakened.

Blood glucose levels obtained during the first two week period were compared with those obtained during the second two week period. Statistical analysis will be performed with student t-test for inter and intra group comparisons for both blood sugar levels and incidence of symptomatic hypoglycemic events.

### **EXAMPLE 2**

Twenty patients with a history of nighttime hypoglycemia, ages 5-16 years, and having had diabetes mellitus for more than one year, participated in the following study. For the first two week period the patients received the standard bedtime snack containing 30 grams of carbohydrate but no uncooked cornstarch. Blood glucose readings were done at 2 a.m. and before breakfast, with an at home glucose meter. During the second two week period, 1/4 to 1/2 of the carbohydrate content of the bedtime snack for each patient was given as uncooked cornstarch in milk. In Table 1 below the mean ( $\pm$ SD) number of hypoglycemic episodes for the 13 subjects (as characterized by a blood glucose reading less than 60 mg/dl) are shown for the 2 a.m. reading and the before breakfast readings.

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**TABLE 1**

	<b><u>14 days Standard</u></b>	<b><u>14 days Cornstarch</u></b>
2 a.m.	2.00 ± 2.12	0.61 ± 0.87
before breakfast	2.61 ± 2.25	0.69 ± 1.03

- 5 Our results suggest that uncooked cornstarch can be used to decrease episodes of nocturnal hypoglycemia in young patients with diabetes mellitus and history of hypoglycemia. This was accomplished without increasing the mean AM blood glucose level, therefore not altering overall glycemic control.
- 10 The foregoing description of the invention is exemplary for purposes of illustration and explanation. It should be understood that various modifications can be made without departing from the spirit and scope of the invention. Accordingly, the following claims are intended to be interpreted to embrace all such modifications.

**CLAIMS**

1. A method for regulating and stabilizing blood glucose levels in humans with Diabetes Mellitus comprising ingesting a complex carbohydrate in the dose of about 0.1 to 1.0 gram per kilogram of body weight.
2. The method of claim 1 wherein the complex carbohydrate is uncooked cornstarch, said uncooked cornstarch being administered in a palatable carrier.
3. The method of claim 2 wherein the dose is from about 0.25 to 0.5 grams per kilogram of body weight.
4. The method of claim 1 wherein the Diabetes Mellitus is Type I and the human further receives a regimen of subcutaneous insulin therapy.
5. The method of claim 1 wherein the Diabetes Mellitus is Type II and the human further receives a regimen of subcutaneous insulin therapy.
6. The method of claim 1 wherein the carrier is a liquid.
7. The method of claim 2 wherein the human receives a bedtime snack containing 30 grams of carbohydrate and the uncooked cornstarch is substituted for from 1/4 to 1/2 of the carbohydrate contained therein.

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8. The method of claim 7 wherein the uncooked cornstarch is contained within a filling for or coating upon the bedtime snack and is sweetened with a non-sugar sweetener.
9. The method of claim 2 wherein the uncooked cornstarch is formulated in 5 gram unit doses.
10. The method of claim 9 wherein the unit doses are formulated for sustained release.
11. The method of claim 1 wherein the blood glucose level is stabilized to 60 mg/dl or greater for at least six hours.
12. The method of claim 2 wherein the blood glucose level is stabilized to 60 mg/dl or greater for at least six hours.
13. A pharmaceutical composition being a unit dose preparation of uncooked cornstarch.